

U.S. Army Center for Health Promotion
and Preventive Medicine

**Wildlife Toxicity Assessment for
2-Nitrodiphenylamine and
4-Nitrodiphenylamine**

APRIL 2006

**Prepared by
Health Effects Research Program
Environmental Health Risk Assessment Program**

**USACHPPM Document No: 87-MA02T6-05B
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**FINAL REPORT
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Acknowledgements

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When referencing this document use the following citation:

Salice, C.J. and G.Holdsworth. 2005. Wildlife Toxicity Assessment for 2- and 4-Nitrodiphenylamine. U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) Document Number 3787-MA02T6-05B, Aberdeen Proving Ground, Maryland.

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Department of the Army
U.S. Army Center for Health Promotion and Preventive Medicine

Wildlife Toxicity Assessment for 2-Nitrodiphenylamine and 4-Nitrodiphenylamine

CAS No. 119-75-5 and 836-30-6

June 2005

1. INTRODUCTION

2-Nitrodiphenylamine (2-NDPA) is a reddish-brown crystalline powder used as a stabilizer for propylene glycol dinitrate (PGD) in "Otto Fuel II", an explosive propellant for torpedoes (ATSDR 1995). The compound constitutes about 1.5 percent of Otto Fuel II; the other major constituent is dibutyl sebacate (22.5 percent). The compound is also used as an ingredient in the U.S. Army's double base solid propellants and, in the civilian sector, as a solvent dye. Little information has been documented about 2-NDPA in secondary sources on industrial hygiene, toxicology or environmental fate and transport. For example, the Hazardous Substances Databank contains no record for the compound. Likewise, 2-NDPA is not included in the U.S. Environmental Protection Agency's Integrated Risk Information System, or in publications of the National Institute of Occupational Safety and Health or the Occupational Safety and Health Administration. Toxicological information on an isomer of 2-NDPA, 4-Nitrodiphenylamine (4-NDPA) is more readily available, and may be a useful surrogate for 2-NDPA toxicity. 4-NDPA is in the form of dark yellow crystals with a faint aromatic odor (Monsanto 1989). This compound is manufactured at a limited number of sites worldwide and is used solely as a chemical intermediate for industrial uses (OECD SIDS 1997). Generally, it is fully consumed in chemical reductive alkylation reactions during manufacture of other products.

This Wildlife Toxicity Assessment summarizes current knowledge of the likely harmful impacts of 2-NDPA and 4-NDPA on wildlife, emphasizing, where possible, threshold doses for the onset of toxicological effects, as described in reports of experimental studies of the compounds. Surveying the threshold dosimetry of the compounds may point to the establishment of toxicity reference values (TRVs); dose levels that could serve as protective exposure standards for all wildlife becoming exposed to either 2-NDPA or 4-NDPA while ranging near affected sites. It should be noted that 4-NDPA is not expected to be prevalent in the environment due to its limited manufacture and typical disposal methods (i.e., residues of 4-NDPA in downstream manufacturing processes are generally incinerated; OECD SIDS 1997). The protocol for the performance of this assessment is documented in the U.S. Army Center for Health Promotion and Preventive Medicine Technical Guide 254, *Standard Practice for Wildlife Toxicity Reference Values* (USACHPPM 2000).

2. TOXICITY PROFILE

2.1 Literature Review

Relevant biomedical, toxicological, and ecological databases were searched electronically May 29, 2002, using DIALOG to identify primary reports of studies and reviews on the toxicology of 2-NDPA. A single search was conducted for the compound with no descriptors. In general, a two-tiered approach was used in which all citations were first evaluated as titles and "key words in context." All available abstracts of those articles selected in the Tier 1 as possibly relevant to TRV development were then evaluated for relevancy in Tier 2. For 2-NDPA, seven articles were marked for retrieval from 80 initial hits, reflecting a paucity of applicable toxicological information on 2-NDPA in the environmental and biomedical literature. Subsequent to these initial searches for 2-NDPA, the TOXNET databases were searched on February 17, 2005 and again on May 20, 2005, using only the compound name "nitrodiphenylamine" and no descriptors. Of 36 hits, 6 articles (one of which was already obtained for 2-NDPA) were marked for retrieval. Four of these articles were relating to toxic effects of 4-NDPA. The Defense Technical Information Center (DTIC) database also was searched using the term 2-nitrodiphenylamine and no hits were obtained. 4-Nitrodiphenylamine also had a profile in the Hazardous Substances Data Bank (HSDB) and a Screening Information DataSets (SIDS) Initial Assessment Report developed for the Organization for Economic Co-operation and Development (OECD). Details of the search strategy and results are documented in Appendix A.

2.2 Environmental Fate and Transport

As summarized in Table 1a, all of the physical-chemical information applicable to the environmental fate and transport of 2-NDPA comes from the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile on Otto Fuel II (ATSDR 1995) and an on-line information sheet posted by the National Toxicology Program Chemical Repository (NTP/Radian 2002). However, the primary focus of the former document is on the major component, PGD, for which comparatively small amounts of 2-NDPA act as a stabilizer. ATSDR (1995) contains some general comments about the potential for 2-NDPA to be disseminated in the environment. For example, the compound has low volatility, suggesting that it is unlikely to be released to the air. Similarly, the solubility of the compound in water is low, suggesting that it will more likely absorb to sediment or soil than leach to groundwater. ATSDR (1995) reports corroborating evidence for this suggestion in a summary of a study of the waste water releases from a U.S. Army ammunition plant. There is a small amount of evidence that 2-NDPA will be broken down in the environment. For example, photolysis of the compound has been demonstrated (ATSDR 1995). Furthermore, Powell et al. (1998) showed that 2-NDPA can be broken down by *Clostridium* species, although the end products were not identified and at least one other carbon source appeared to be essential for growth.

Table 1a. Summary of Physical-Chemical Properties of 2-Nitrodiphenylamine

CAS No.	119-75-5
Molecular weight	214.22
Color	Reddish-brown
Physical state	Crystalline
Melting point	75.5 °C
Boiling point	No data
Odor	Faint, ethereal
Solubility in water	<1 mg/L at 20-25 °C: soluble in ethanol, acetone, dimethyl sulfoxide
Partition coefficients:	
Log K _{ow}	4.9 x 10 ⁻¹
Log K _{oc}	No data
Vapor pressure at 25 °C	1 x 10 ⁻⁵ mm Hg
Henry's Law constant at 25 °C	No data
Conversion factors	1 ppm = 8.76mg/m ³ 1 mg/m ³ = 0.114 ppm

Sources: NTP/Radian (2002), ATSDR (1995)

The physical-chemical data applicable to the environmental fate and transport of 4-NDPA are presented in Table 1b, and primarily come from an UNEP Publication titled *Benzenamine, 4-nitro-N-phenyl: CAS No: 836-30-6* (OECD SIDS 1997), the Material Safety Data Sheet (MSDS) from Monsanto Company (Monsanto 1989), and the Hazardous Substance Data Bank (HSDB 2005). Given the limited production, use, and disposal methods, environmental release of 4-NDPA would occur primarily during the manufacturing process. However, these releases are predicted to be negligible due to the physical properties of the compound (OECD SIDS 1997). In studies cited in OECD SIDS (1997), 4-NDPA was not readily biodegradable (i.e., it was observed to have no biodegradation, no aerobic biodegradability or chemical degradation after 8 weeks in river water and no ultimate degradation to CO₂ after up to 35 days) and its partition coefficient (LogK_{ow} of 3.82) indicates a potential for bioaccumulation. As with 2-NDPA, the physical properties of 4-NDPA suggest that this chemical would partition to soil and sediment rather than leach to groundwater. 4-NDPA is likely to be persistent and is only slowly photodegradable (i.e., photo transformation in water of about 7 % in 7 days and a half-life of 70 days). It was noted in OECD SIDS (1997) that although 4-NDPA is predicted to be persistent in the environment, no environmental residues from production activities have been detected.

Table 1b. Summary of Physical-Chemical Properties of 4-Nitrodiphenylamine

CAS No.	836-30-6
Molecular weight	214.23
Color	Dark yellow
Physical state	Crystalline

Table 1b. Summary of Physical-Chemical Properties of 4-Nitrodiphenylamine

Melting point	133.5 °C
Boiling point	211°C (HSDB 2005) or 343 °C (OECD SIDS 1998)
Odor	Faint, aromatic
Solubility in water	4.1 mg/L at 24 °C: insoluble in water, soluble in alcohol, acetic acid, sulfuric acid
Partition coefficients:	
Log K _{ow}	3.82 at 25 °C
Log K _{oc}	No data
Vapor pressure at 25 °C	<0.15 mm Hg
Henry's Law constant at 25 °C	No data
Conversion factors	1 ppm = 8.76mg/m ³ 1 mg/m ³ = 0.114 ppm

Sources: HSDB (2005), OECD SIDS (1997), Monsanto (1989)

2.3 Summary of Mammalian Toxicity

2.3.1 Mammalian Oral Toxicity

2.3.1.1 Mammalian Oral Toxicity - Acute

Few data were identified that address the acute lethality of these compounds to mammals. However, an abstract by Scharman and Rosencrance (1994) cites a manufacturer's data sheet for 2-NDPA in which an oral median lethal dose (LD₅₀) in rats of 12 g/kg (or 12,000 mg/kg) is given. This suggests an overall lack of acute oral toxicity for 2-NDPA, although the abstract itself summarizes a case report of two truck washers who became ill while cleaning out the tank of a vehicle that had been used to transport the compound. Cyanosis with accompanying methemoglobinemia appeared to be the primary reaction. As with 2-NDPA, 4-NDPA was not observed to be acutely toxic. The oral LD₅₀ for rats was reported as greater than 7,940 mg/kg (Monsanto 1989 and OECD SIDS 1997). Of 3 males and 2 females dosed at 7,940 mg/kg, no deaths occurred (OECD SIDS 1997).

2.3.1.2 Mammalian Oral Toxicity - Subchronic

No subchronic data for 2-NDPA were located. However, initial toxicity studies using 4-NDPA were conducted by Monsanto Company in 1984 and submitted to the United States Environmental Protection Agency (USEPA 1992). Groups of 5 male and 5 female Sprague-Dawley rats were fed dietary doses of 0, 2,000, 5,000, 10,000, and 20,000 ppm 4-NDPA for one month. Using the mean food consumption rate (g/kg body weight/day) reported for males and females in each dose group, these doses were approximately equal to 0, 195, 469, 943, and 1,761 mg/kg/d. Although no deaths occurred at any of the

dose levels, a dose-dependent decrease in body weights of both males and females was observed in the three highest dose groups relative to controls. This difference was statistically significant in the two highest dose groups. Food consumption also was reduced in the 10,000 and 20,000 ppm dose groups, though the body weight to food ingestion ratio was similar to controls. In a paired study, the authors fed control rats the same amount of food as was eaten by rats in the 20,000 ppm group and observed a similar reduction in body weight. Therefore, it was concluded that poor diet palatability, especially among males, was a factor in the observed body weight reductions. Yellow/orange urine and yellow fur were observed in all dose levels, though this was not considered a toxic effect. Finally, renal tubular cysts and casts were observed in males at the 5,000, 10,000, and 20,000 ppm dose levels. No renal effects were noted at the 2,000 ppm treatment. Therefore, the authors concluded that the kidney is the target organ for 4-NDPA. The study does not report no observed adverse effects levels (NOAELs) and lowest observed adverse effects levels (LOAELs). Because this study occurred over a one month period (less than 10 percent of the life span of the test species, but greater than 14 days) it is considered to be equivalent to a subchronic study (USACHPPM 2000). Based on the data presented, a subchronic NOAEL of 195 mg/kg/d (2,000 ppm dose level) and a subchronic LOAEL of 469 mg/kg/d (5,000 ppm dose level) for kidney toxicity (presence of cysts/casts) can be derived.

A second subchronic study conducted by Monsanto is reported in OECD SIDS (1997) and in the MSDS for 4-NDPA (Monsanto 1989). In this study, 30 male and 30 female Sprague-Dawley rats were given 0, 800, 2,000, and 5,000 ppm 4-NDPA for 90 days. No data on the body weights and food consumption rates were provided in this secondary source; however, it is noted that the 800 ppm level is equivalent to 57 mg/kg/d (OECD SIDS 1997). Based on these data, a food consumption rate of 71.25 g food/kg body weight/day was calculated and used to determine daily doses of 143 and 356 mg/kg/d for the 2,000 and 5,000 ppm dose groups, respectively. Observed effects included decreased body weight gain, histopathological effects on kidneys and spleen, slight anemia, and increased methemoglobin values (Note: OECD SIDS [1997] does not indicate at which dose levels each of these effects occurred). No toxic effects were observed at the 800 ppm exposure level. Therefore, the 800 ppm level (57 mg/kg/d) represents a subchronic NOAEL and the 2,000 ppm dose group (143 mg/kg/d) represents a subchronic LOAEL.

2.3.1.3 Mammalian Oral Toxicity – Chronic

No chronic mammalian oral toxicity data were located.

2.3.1.4 Mammalian Oral Toxicity - Other

Monsanto also conducted a developmental study using 4-NDPA in 1991. The results of this study were submitted to the USEPA (1991) and are also reported in a published abstract (Bannister et al. 1992). Groups of 25 female rats were dosed with 250, 1,000, and 3,000 mg 4-NDPA /kg/d and a dose volume of 10 mL/kg during days 6 through 15 of gestation. A control group of 25 female rats was dosed with corn oil at the same volume during the same period. Females were observed for clinical signs of toxicity, and body weights and food consumption were measured on gestation days 0, 6, 9, 12, 16, and 20. Fetuses were removed via cesarean section on gestation day 20 and were weighed, sexed, and examined for external, skeletal, and visceral abnormalities. Maternal toxicity occurred in the two highest dose groups, with eight females (32 %) in the 3,000 mg/kg/d and one female (4 %) in the 1,000 mg/kg/d dose groups found dead during the treatment period. Additionally, clinical signs of toxicity (e.g., no or few feces) and dose dependent reductions in body weight gain and food consumption were observed at these two dose levels. No signs of maternal toxicity were observed at the 250 mg/kg/d dose level. Fetal weights were significantly reduced within the 3,000 mg/kg/d dose group. There were also a significantly increased number of litters with 27 presacral vertebrae in the 3,000 mg/kg/d dose group, and a slight, but not statistically significant, increase in number of fetuses/litters with 14th full ribs in both the 1,000 and 3,000 mg/kg/d dose groups. Based on these findings, the authors considered the 250 mg/kg/d dose level to be the NOAEL for a lack of effects to the dams or fetuses.

2.3.1.5 Studies Relevant for Mammalian TRV Development for Ingestion Exposures

The developmental studies reported in USEPA (1991) and Bannister et al (1992) evaluated sensitive effects in a developmental study design. Because this study was conducted during a sensitive life stage and adverse effects (i.e., decreased fetal body weights) were observed, this study is considered to be equivalent in value to data collected using a chronic study design (USACHPPM 2000). Therefore, the 250 mg/kg/d dose group represents a chronic NOAEL and the 1,000 mg/kg/d dose level would represent the chronic LOAEL. Chronic studies for 2-NDPA were not available; however, given the low acute toxicity of 2-NDPA, it is unlikely that further studies would provide useful results (i.e. beyond the limit value).

Based on the available studies, the primary target organs for 4-NDPA are the kidneys (USEPA 1992 and OECD SIDS 1997) and blood (OECD SIDS 1997). Additionally, effects were found at high exposures in fetuses from dams dosed with 4-NDPA (Table 2, Figure 1). These studies represent acute, subchronic, and chronic exposure, though the Sprague-Dawley laboratory rat is the only species that has been studied. Effects considering the magnitude and means of exposure are consistent among the three

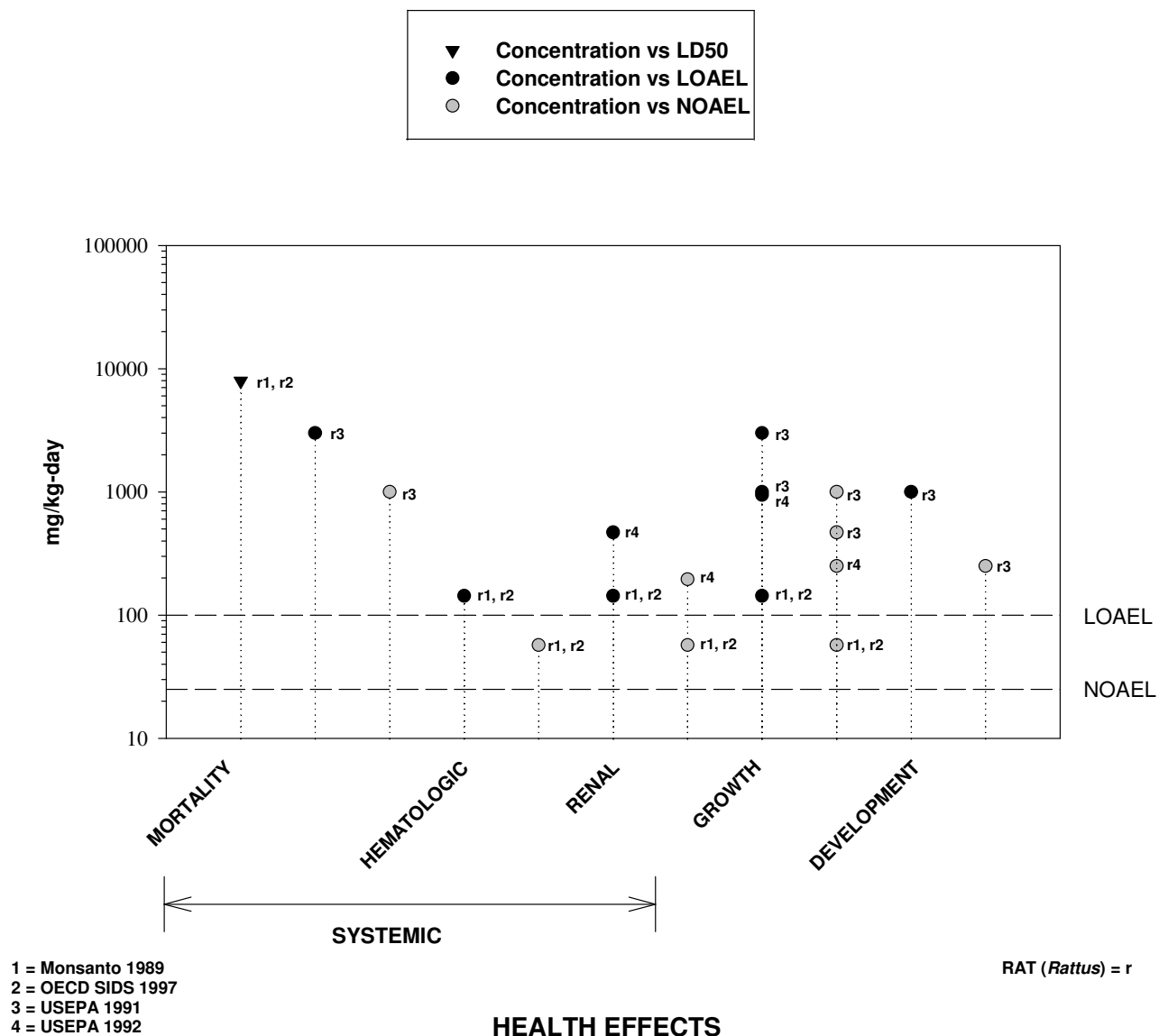
studies. Therefore, all three studies are considered sufficient to derive class-specific TRVs for 4-NDPA. No data on subchronic or chronic exposures to 2-NDPA were located. Acute studies alone were not considered relevant for TRV development; however, they indicate that both 2-NDPA and 4-NDPA are not highly toxic.

Table 2. Summary of Relevant Mammalian Data for TRV Derivation (4-NDPA)

Test Type	Study	Test Organism	Test Duration	Test Results		
				NOAEL (mg/kg/d)	LOAEL (mg/kg/d)	Effects Observed at the LOAEL
Developmental	USEPA, 1991	Rat (Sprague-Dawley)	10 d (exposure during gestation)	250 (♀)	1,000 (♀)	Maternal mortality, reduced body weight gain, reduced food consumption, and clinical signs of toxicity (e.g., no or few feces).
	USEPA, 1991	Rat (Sprague-Dawley)	10 d (exposure during gestation)	250 (fetal)	1,000 (fetal)	Increased incidence of 14th full ribs. Decreased body weights at 3,000 mg/kg/d.
Subchronic	USEPA, 1992	Rat (Sprague-Dawley)	30 d	195 (♂)	469 (♂)	Renal tubular cysts and casts in males
				469 (♀)	943 (♀)	Dose-dependent decrease in body weights of both males and females.
	Monsanto, 1989 and OECD SIDS, 1997 ^a	Rat (Sprague-Dawley)	90 d	57 (♂+♀)	143 (♂+♀)	Decreased body weight gain, histopathological effects on kidneys and spleen, slight anemia, and increased methemoglobin values.

^a Secondary sources.

Figure 1.

4-NITRODIPHENYLAMINE: HEALTH EFFECTS TO MAMMALS

2.3.2 Mammalian Inhalation Toxicity

One dust inhalation study using 4-NDPA is reported in Monsanto (1989) and OECD SIDS (1997). In this study, 10 male and 10 female Sprague-Dawley rats were exposed to 4-NDPA by whole body dust inhalation at 8.5, 29, and 52 mg/m³ for 6 hours per day, 5 days per week for 21 days. Increased methemoglobin, absolute and relative liver weights, and hematological changes were observed at the 29 and 52 mg/m³ dose levels. No adverse effects were noted at the 8.5 mg/m³ dose level. Although OECD SIDS (1997) reports this as a subacute study, treatment occurred over less than 10 percent of the life span of the test species, but for greater than 14 days. Therefore, this study is considered to be subchronic (USACHPPM 2000), with the 8.5 mg/m³ dose level representing the subchronic NOAEL and the 29 mg/m³ dose level representing the subchronic LOAEL.

2.3.3 Mammalian Dermal Toxicity

A dermal LD₅₀ of greater than 7,940 mg/kg has been reported (Monsanto 1989 and OECD SIDS 1997). No deaths occurred at this level, although only one male and one female were tested (OECD SIDS 1997).

2.4 Summary of Avian Toxicology

No data for birds were found.

2.5 Summary of Amphibian Toxicology

No data for amphibians were found.

2.6 Summary of Reptilian Toxicology

No data for reptiles were found.

3. RECOMMENDED TOXICITY REFERENCE VALUES

3.1 Toxicity Reference Values for Mammals

3.1.1 TRVs for Ingestion Exposures for the Class Mammalia

Data from 4- and 2-NDPA exposures suggest that these compounds are relatively non-toxic. Limit test criteria were exceeded for both compounds (limit test values are 2-5g/kg; if met, further studies are not normally conducted (USEPA 2002). However, further data were collected for the more toxic of the two isomers (4-NDPA) with most findings in general agreement. Feeding studies suggested 4-NDPA had reduced palatability, and therefore exposures that may cause adverse effects are highly unlikely. Nevertheless, data collected from the developmental study (USEPA 1991) can be useful in deriving a TRV protective of any adverse effects from chronic exposures useful for risk assessment purposes. The

treatment occurred during a sensitive life stage, and maternal toxicity was evaluated. Adverse effects on maternal survival, maternal and fetal growth (body weight gain, food consumption, and fetal body weight), and fetal development (increased incidence of 27 presacral vertebrae and 14th full ribs) of rats exposed to 4-NDPA were observed. Decreased growth in rats fed 4-NDPA was also observed in the subchronic studies; however, this effect may be a consequence of reduced palatability. Both decreased maternal survival and reduced maternal and fetal growth were used to determine the TRV because these endpoints have the potential to be ecologically important. As indicated in the Standard Practice, Section 2.2 (USACHPPM 2000), mortality, reproduction, development, and growth are toxicological endpoints that are relevant to the health and ecology of the whole organism. Therefore, the LOAEL for rats based on the USEPA (1991) study is 1,000 mg/kg/d. The highest NOAEL within the same species and endpoints was 250 mg/kg/d, reported by the same authors.

Despite the relevancy of the toxic endpoints, the three studies relevant for TRV derivation do not meet the minimum data set requirement of the Standard Practice, Section 2.2 (USACHPPM 2000). Namely, the studies do not provide data for three or more mammalian species and do not represent two different taxonomic orders. Therefore, TRVs based on an approximation of the NOAEL and LOAEL were developed for Class Mammalia using uncertainty factors (UFs). Because only one species is represented, an UF of 10 was applied to the NOAEL and LOAEL (250 and 1,000 mg/kg/d, respectively) to account for interspecific variability. Table 3 presents the selected TRVs. A medium level of confidence has been assigned to these TRVs because the base of data suggests that both compounds are relatively non-toxic in monogastric rodents and these values are indeed conservative. However, there is uncertainty given that there are no data on hindgut fermenting or ruminant species that may respond differently from exposure. Given that the data from the 4-NDPA studies seem to be more toxic than 2-NDPA, the TRVs derived for 4-NDPA may be used as a surrogate until such time as additional 2-DNPA toxicity data become available.

Table 3. Selected Ingestion TRVs for the Class Mammalia

TRV	Dose mg/kg/d	Confidence
NOAEL-based	25	Medium
LOAEL-based	100	Medium

3.1.2 TRVs for Ingestion Exposures for Mammalian Foraging Guilds

TRVs specific to particular guild associations (e.g., monogastric rodents) have not yet been derived. However, the class-specific TRVs shown in Table 3 may be considered to apply to small herbivorous mammals because rats are members of this guild. As with the class-specific TRVs, only one species is represented so confidence in the TRVs is medium. Data to derive TRVs for other guild associations (e.g., carnivorous mammals) is not available at this time.

3.1.3 TRVs for Inhalation Exposures for the Class Mammalia

One study (reported in secondary sources Monsanto 1989 and OECD SIDS 1997) evaluated the inhalation toxicity of 4-NDPA to mammals. This study is considered subchronic, and does not meet the minimum data set requirements (i.e., only one species and one taxonomic order represented, and no chronic NOAEL or LOAEL). As a consequence, UFs were applied to the NOAEL and LOAEL from the study. For the NOAEL (8.5 mg/m^3), an interspecific UF of 10 and a subchronic NOAEL-to-chronic NOAEL UF of 10 were applied, whereas an interspecific UF of 10 and a subchronic LOAEL-to-chronic LOAEL UF of 4 were applied to the LOAEL (20 mg/m^3). Because the study was subchronic, only one species was evaluated, and there is uncertainty associated with the relevance of the toxicity endpoint to the reproduction, growth, or survival of the organism, confidence in the TRVs derived is very low. As with oral toxicity, no data for 2-NDPA were available; thus, TRVs developed for 4-NDPA may be used as a surrogate pending further toxic evaluation of 2-NDPA.

Table 4. Selected Inhalation TRVs for the Class Mammalia

TRV	Exposure mg/m^3	Confidence
NOAEL-based	0.085	Low
LOAEL-based	0.725	Low

3.1.4 TRVs for Dermal Exposures for the Class Mammalia

Sufficient data required for development of dermal TRVs for Class Mammalia are not available. However, the high reported LD_{50} ($>7,940 \text{ mg/kg}$) for 4-NDPA suggests that this compound has a low dermal toxicity to mammals. No dermal toxicity data were available for 2-NDPA.

3.2 Toxicity Reference Values for Birds

Not available at this time.

3.3 Toxicity Reference Values for Amphibians

Not available at this time

3.4 Toxicity Reference Values for Reptiles

Not available at this time

4. IMPORTANT RESEARCH NEEDS

Toxicological data for 2-NDPA are minimal, but suggest both compounds are relatively non-toxic through exceeding limit test requirements (USEPA 2004). More subchronic data in additional species would help increase confidence in TRV estimates. However, there are no data for hindgut fermenting or ruminant species. These species may have a different capacity to absorb and assimilate NDPA. However, given the reduction in palatability, potential for significant exposure is low.

No data were available for other classes of wildlife (birds, amphibians, and reptiles). Research is desirable for testing in these species, first in regards to acute toxicity and to corroborate these findings with the mammalian data to determine if further studies are necessary. Given indications of reduced palatability, ecological evaluations regarding loss of a food resource may be important, but depends upon spatial heterogeneity of NDPA in the environment. Furthermore, occurrence of the NDPA isomers is very low. Currently, there are no compelling data that NDPA isomers are prevalent to justify a robust development of toxicity data. There are very sites that have worked with these compounds a rarer still positive environmental data of NDPA compound in media. Until a greater need can be established, we recommend no additional toxicity studies be conducted..

5. REFERECES

- Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological Profile for Otto Fuels II. U.S. Department of Health and Human Services, Atlanta, GA.
- Bannister, R. M., D.W. Brewster, D. E. Rodwell, R. E. Schroeder, and J. W. Barnett, Jr. 1992. Developmental toxicity studies in rats with 4-aminodiphenylamine (4-ADPA) and 4-nitrodiphenylamine (4-NDPA). *Toxicologist* 12(1):103.
- Monsanto, Inc. (Monsanto). 1989. Material Safety Data Sheet for 4-Nitrodiphenylamine. In USEPA. 1991. *Follow-up Information: Teratology Study in Rats with 4-Nitrodiphenylamine (Final Report) with Attachments and Cover Letter Dated 042391*. EPA/OTS: Doc #89-910000119. April.
- National Toxicology Program Chemical Repository (NTP/Radian). 2002. On-line. Accessed at http://157.98.10.135/NTP_Reports/NTP_Chem_HS-HTML.NTP_Chem/Radian/119-75-5.html.
- OECD SIDS. 1997. *SIDS Initial Assessment Report for SIAM 8: Benzenamine, 4-nitro-N-phenyl* CAS No: 836-30-6. Brussels, Belgium. July. Online at <http://cs3-hq.oecd.org/scripts/hpv/>.
- Powell, S., P.D. Franzmann, R. Cord-Ruwish, and S. Toze. 1998. Degradation of 2-nitrodiphenylamine, a component of Otto Fuel II, by *Clostridium* spp. *Anaerobe*. 4: 95-102. (abstract retrieved from <http://www.sciencedirect.com>).
- Scharman, E.J., and J.G. Rosencrance. 1994. Exposure to 2-nitrodiphenylamine. *Vet. Hum. Toxicol.* 36: 345.
- U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM). 2000. *Standard Practice for Wildlife Toxicity Reference Values*, Technical Guide 254.
- U.S. Environmental Protection Agency (USEPA). 1991. *Follow-up Information: Teratology Study in Rats with 4-Nitrodiphenylamine (Final Report) with Attachments and Cover Letter Dated 042391*. EPA/OTS: Doc #89-910000119. April.
- U.S. Environmental Protection Agency (USEPA). 1992. *Initial Submission: Four Week Study of 4-Nitrodiphenylamine Administered in the Diet to Sprague-Dawley Rats with Cover Letter Dated 080792*. EPA/OTS: Doc#88-920007690. August.
- U.S. Environmental Protection Agency (USEPA). 2004. Health Effects Test Guidelines: Acute Oral Toxicity. OPPTS 870.1100, EPA 712-C-02-190. U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Washington, DC. December.

APPENDIX A

LITERATURE REVIEW

1. A search in DIALOG for 2-nitrodiphenylamine was conducted May 29, 2002, with the following files examined:

File 155 MEDLINE, File 76 Life Sciences Collection, File 185 Zoological Record Online, File 5 Biosis Previews, File 73 EMBASE, Files 34 and 434 SciSearch

The structure was as follows: For

All Receptors:

- * The expression 2-nitrodiphenylamine and its CAS Number
- * RD (Reduce Duplicates)

As noted in Section 2.1, 80 hits on 2-nitrodiphenylamine were obtained in initial search, of which seven were selected for retrieval.

2. A search in DTIC was conducted February 2005. No hits for 2-nitrodiphenylamine were obtained.

3. A search in TOXNET for nitrodiphenylamine was conducted February 17, 2005 and again on May 20, 2005.

As noted in Section 2.1, 36 hits on nitrodiphenylamine were obtained in the initial search of TOXLINE Special, of which six were selected for retrieval.

4. A search of the Hazardous Substances Data Bank (HSDB) for 4-Nitrodiphenylamine resulted in 1 hit.

5. An Internet search resulted in retrieval of a Screening Information DataSets (SIDS) Initial Assessment Report developed for the Organisation for Economic Co-operation and Development (OECD) and found at <http://cs3-hq.oecd.org/scripts/hpv/>.